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(54) Title: A PROCESS FOR PREPARING 1-METHYL-3-PHENYL-PIPERAZINE

(57) Abstract: A process for preparing 1-Methyl-3-phenyl-piperazine, which comprises: (i) mixing 1-Benzyl-2-phenyl-piperazine with formic acid solution while stirring and then with formaldehyde solution and heating the mixture to a temperature of 70 °C to 80 °C for 50 to 70 minutes; (ii) reheating the obtained solution of Step (i) to a temperature of 90 to 95 °C for 50 to 70 minutes; (iii) checking the obtained mass of Step (ii) for the absence of the starting material (TLC system, Toluene: IMS=6:4) and treating with sodium hydroxide solution while stirring for 50 to 70 minutes at a temperature of below 25 °C and filtering; (iv) washing the product of Step (iii) with water and drying to obtain 1-Benzyl-4-methyl-2-phenyl piperazine; (v) adding the product of Step (iv) with acetic acid taken in hydrogenator in the presence of palladium-carbon catalyst under nitrogen atmosphere while continuously stirring the mixture for about 6 to 10 hours keeping hydrogen pressure of 3.5 to 4.0 kg/cm^2; (vi) checking the product of Step (v) for the absence of the starting material (TLC system, Ethyl acetate: Methanol = 1:1) and filtering under nitrogen and distilling acetic acid completely under vacuum; (vii) stirring the residue of Step (vi) with demineralised water and stirring with sodium hydroxide solution at a temperature up to 25 °C and extracting at least twice with hexane; (viii) concentrating the hexane layer to the mass of Step (vii) followed by stirring and filtering at a temperature of O to 5 °C, (ix) treating the product of Step (viii) with chilled hexane and drying in an air oven to obtain 1-Methyl-3-phenyl-piperazine.

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Field of Invention

At the very outset, to put it succinctly, the present invention pertains to the pharmaceutical industry in general novel process for preparing 1-Methyl-3-phenyl piperazine without impurities.

Prior Art

For preparation of the drug substance viz., Mirtazapine which is an anti depressant drug, 1-Methyl-3-phenyl piperazine is a key intermediate. Long time ago i.e., on September 20, 1998, the preparation of 1-Methy-3-phenyl piperazine was reported in U.S. Patent 4772705 wherein its preparation was reported as starting from ethylene diamine and ethyl a-bromophenyl acetate in absolute ethanol to give 3-phenyl-2-piperazinone which on reduction with lithium aluminium hydride in anhydrous ether gave 2-phenyl piperazine which was methylated with methyl iodide in presence of acetone and tricthylamine and isolated as its hydrochloride in 54% yield. Methylation of 2-phenyl piperazine by this method gives undesired side products, which are difficult to be eschewed or removed. The above process is time consuming and expensive. Besides the obtained process is full of impurities.

Summary of the Invention

It has, therefore, been long felt need to develop a process which is easy and cost effective.

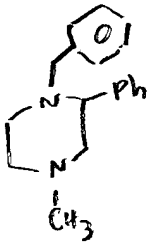
According to the present invention there is provided a process for preparing 1-Methyl-3-phenyl-piperazine, which comprises:

(i) mixing 1-Benzyl-2-phenyl piperazine with formic acid solution while stirring and then with formaldehyde solution and heating the mixture to a temperature of 70°C to 80°C for 50 to 70 minutes;

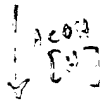
(ii) reheating the obtained solution of Step (i) to a temperature of 90 to 95°C for 50 to 70 minutes;

(iii) checking the obtained mass of Step (ii) for the absence of the starting material (TLC system, Toluene: IMS = 6:4) and treating with sodium hydroxide solution while stirring for 50 to 70 minutes at a temperature of below 25°C and filtering;

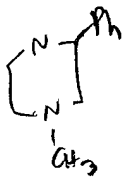
(iv) washing the product of Step (iii) with water and drying to obtain 1-Benzyl-4-methyl-2-phenyl piperazine;



(v) adding the product of Step (iv) with acetic acid taken in hydrogenator in the presence of palladium-carbon catalyst under nitrogen atmosphere while continuously stirring the mixture for about 6 to 10 hours keeping hydrogen pressure of 3.5 to 4.0kg/cm^2;



(vi) checking the product of Step (v) for the absence of the starting material (TLC system, Ethyl acetate: Methanol = 1:1) and filtering under nitrogen and distilling acetic acid completely under vacuum;



(vii) stirring the residue of Step (vi) with demineralised water and stirring with sodium hydroxide solution at a temperature up to 25°C and extracting at least twice with hexane;

(viii) concentrating the hexane layer to the mass of Step (vii) followed by stirring and filtering at a temperature of 0 to 5°C;

(ix) treating the product of Step (viii) with chilled hexane and drying in an air oven to obtain 1-Methyl-3-phenyl-piperazine.

In the developed process the retained 1-Methyl-3-phenyl piperazine is derived sans impurities. Besides, as stated earlier, this 1-Methyl-3-phenyl piperazine is highly imperative for preparation of the anti-depressant drug, which is known as Mirtazapine. In the obtained process 1-Methyl-3-phenyl piperazine is free from impurities.

We shall now describe the invention in detail: -

1. Preparation of 1-Benzyl-4 methyl-2-phenyl piperazine - To put it succinctly, 1-Benzyl-2 phenyl piperazinem (355.2 g. 1.41 moles) gets added to formic acid's stirred solution (85% w/w/; 190g 3.51 moles), which is being followed by fomaldehyde solution (35% w/w/; 145g. 1.69 moles). The contents get heated to and maintained for one hour at 70 to 80^{0}C. Then, contents are heated to and maintained for 50 to 70 minutes at 90 to 95^{0}C. A sample of the reaction mass is checked for the absence of the starting material (TLC system, Toluene: IMS = 6:4). Then the reaction mass gets added to sodium hydroxide solution (5% w/v; 2800 ml) by maintaining the temperature below 25^{0}C. The contents get stirred for one hour and thereby filtered. The product is then washed with water (1000 ml), sucked well and dried to a constant weight at 50 to 55^{0}C to yield 361g of the product (m.p 73-76^{0}C, yield 96.3%). The material then gets directly taken sans further purification to the next stage.

2. Preparation of 1-Methyl-3-phenyl piperazine – 1-Benzyl-4-methyl-2-phenyl piperazine (200g), 5% palladium-carbon catalyst (10g, 50% wet) and Acetic acid (1000 ml), which is taken in hydrogenator, are added under nitrogen atmosphere. The contents are then stirred under 3.5 to 4.0

kg/cm^2 hydrogen pressure for 6 to 10 hours. A sample of the reaction mass is checked for the absence of the starting material (TLC system, Ethyl acetate: Methanol=1:1). The reaction mass gets filtered under nitrogen atmosphere. Acetic acid is distilled completely under vacuum, demineralised water (300 ml) is added to the residue and to this under stirring sodium hydroxide solution (50% w/v, 400ml) gets added maintaining the temperature below 25^{0}C. The contents are then extracted twice with hexane (1000 ml and 500 ml). The hexane layer is concentrated to 200 ml, cooled 0 to 5^{0}C, stirred for 50 to 70 minutes at 0 to 5^{0}C and filtered. The product is then washed with chilled hexane (50 ml), sucked well dried to a constant weight in an air oven to yield 106g of the product, (m.p. 53 to 55^{0}C, 80.1% yield).

The foregoing description is only illustrative of the present invention it is not intended that the invention be limited thereto. Many other specific embodiments of the present invention will be obvious and apparent to one skilled in the art from the foregoing disclosure. All substitution, changes, alterations and modification of the present invention which come within the scope of the following claims are to which the present invention is readily susceptible without departing from the spirit of the invention.

CLAIMS :

1. A process for preparing 1-Methyl-3-phenyl-piperazine, which comprises:

(i) mixing 1-Benzyl-2-phenyl piperazine with formic acid solution while stirring and then with formaldehyde solution and heating the mixture to a temperature of 70^{0}C to 80^{0}C for 50 to 70 minutes;

(ii) reheating the obtained solution of Step (i) to a temperature of 90 to 95^{0}C for 50 to 70 minutes;

(iii) checking the obtained mass of Step (ii) for the absence of the starting material (TLC system, Toluene: IMS = 6:4) and treating with sodium hydroxide solution while stirring for 50 to 70 minutes at a temperature of below 25^{0}C and filtering;

(iv) washing the product of Step (iii) with water and drying to obtain 1-Benzyl-4-methyl-2-phenyl piperazine;

(v) adding the product of Step (iv) with acetic acid taken in hydrogenator in the presence of palladium-carbon catalyst under nitrogen atmosphere while continuously stirring the mixture for about 6 to 10 hours keeping hydrogen pressure of 3.5 to 4.0kg/cm^2;

(vi) checking the product of Step (v) for the absence of the starting material (TLC system, Ethyl acetate: Methanol = 1:1) and filtering under nitrogen and distilling acetic acid completely under vacuum;

(vii) stirring the residue of Step (vi) with demineralised water and stirring with sodium hydroxide solution at a temperature up to 25^{0}C and extracting at least twice with hexane;

(viii) concentrating the hexane layer to the mass of Step (vii) followed by stirring and filtering at a temperature of 0 to 5^{0}C;

(ix) treating the product of Step (viii) with chilled hexane and drying in an air oven to obtain 1-Methyl-3-phenyl-piperazine.

2. The process as claimed in Claim 1, which involves protection and deportection of one of the nitrogen atoms of the peperazine ring before and after methylation.

3. The process as claimed in Claim 1, which utilizes formic acid and formaldehyde for methylation.

4. The process as claimed in Claim 1, which utilizes acetic acid as the solvent for debenzylation.

5. The process as claimed in Claim 1, which utilizes hexane as solvent for the purification of 1-Methyl-3-phenyl piperazine.

6. 1-Methyl-3-phenyl piperazine wherever prepared by process as claimed in any one of Claims 1 to 5 or otherwise thereof.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/IN 02/00117

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D241/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 772 705 A (R. SCHMIESING) 20 September 1988 (1988-09-20) cited in the application column 12; example 4	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2002	11/09/2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4772705 A	20-09-1988	EP 0300074 A1	25-01-1989